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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,343	04/11/2005	Jacques Mallet	BJS-3665-122	3751

23117 7590 06/26/2008
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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
06/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,343	MALLET ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,36,43-49,51-54 and 57-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,36,43-49,51-54 and 57-67* is/are rejected.

7)☒ Claim(s) *58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 31, 2008 that includes a response to the Final Office Action dated August 3, 2007, has been entered. Claims 35, 36, 43-49, 51-54 and 57-67 are pending in the Application. Claims 35, 43-46, 54, 58 and 64-67 have been amended, and claims 50, 55 and 56 cancelled. No claims were newly added.

Claims 35, 36, 43-49, 51-54 and 57-67 are currently under examination.

New Claim Objection

Claim 58 is objected as failing to clearly distinguish or further limit the method steps of base claim 57. An amendment of the claim to recite: "The method of claim 57, wherein step a) comprises providing a plasmid or a recombinant viral vector for *in vitro* or *ex vivo* transgene delivery into ...." and deleting step b) would be remedial.

Response to Claim Rejections - 35 USC § 112, Written Description

Claims 43-46 and 64-67 were rejected under 35 U.S.C.§112, first paragraph, as failing to comply with the written description requirement, in the previous office action dated August 3, 2007. In view of Applicants' amendment of the claims, deleting language directed to functional fragments of SEQ ID NOS: 1-4 and portions of various regulatory elements, obviating the ground of rejection, the rejection is hereby withdrawn.

Response and New Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 35, 43-46, 54-56 and 64-67 stand rejected, and claims 36, 57 and 58 are newly rejected under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide an enablement for the full scope of the invention. Applicants' cancellation of claims 55 and 56 renders their rejection moot. In view of Applicants' amendment of claims 64-67, deleting language directed to portions of various regulatory elements and obviating the ground of rejection, the rejection of claims 64-67 is hereby withdrawn. The rejection set forth on p. 4 of the office action dated November 14, 2006 and pp. 3-4 of the office action dated August 3, 2007 is maintained for claims 35, 43-46, and 54, and further applied to claims 36, 57 and 58 for reasons of record.

Applicants traverse the rejection, stating that claim 35 has been amended to include the details of claim 50 and claim 54 specifies that the vector is for *in vitro* or *ex vivo* transgene delivery. Applicants argue that the attached post-filing art of Brun et al. is submitted as evidence confirming the efficiency of two different kinds of vectors, i.e. plasmids and recombinant viruses.

Applicants' arguments have been fully considered, but are not found persuasive. Applicants' claim amendments address the grounds for rejection only in part. With regard to the post-filing art of Brun et al., MPEP 2164.05(a), the specification must be enabling as of the filing date. A later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling. Moreover, the publication describes delivery of plasmid and viral vectors into cell lines *in vitro*, and only postulates their intended use for gene therapy.

While the term "suitable" has been deleted from claim 54, directed to *in vitro* or *ex vivo* transgene delivery into mammalian cells, the term is still present in base claim 35, and claim 58. As previously indicated, a vector suitable for *in vitro* delivery does not preclude its use for *in vivo* delivery. Further, claim 54 continues to recite a composition comprising a pharmaceutically acceptable carrier or excipient, and when the claim is given its' broadest reasonable interpretation, in view of the as filed specification that describes using such a composition to treat a human disease by gene therapy or cell therapy, the claim would not be limited to *in vitro* use. Claims 54 and 58 are further

directed to any vector type, and as indicted in the previous office action, the specification is not enabling for the broad family of vectors (that include a plasmid, a cosmid, an artificial chromosome, an episome etc.) as gene therapy compositions for treating human disease.

Therefore, the rejection of claims 35, 43-46 and 54 is maintained and further applied to claims 36, 57 and 58 for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 103

Claims 35, 36 and 46 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538). Claim 43 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538), and further in view of Ramezani et al. (Mol. Ther. 2:458-469; 2000). Claims 40, 44, and 64-65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Paulding et al. (J. Biol. Chem. 274:2532-2538) and Ramezani et al. (Mol. Ther. 2:458-469; 2000), and further in view of Rogers et al. (J. Biol. Chem. 274:6421-6431; 1999). Claims 41-42, 45-51, and 66-67 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view Paulding et al. (J. Biol. Chem. 274:2532-2538) and Ramezani et al. (Mol. Ther. 2:458-469; 2000), and Rogers et al. (J. Biol. Chem. 274:6421-6431; 1999), and further in view of Aronov et al. (J. Mol. Nerurosci., 12:131-145; 1999). Claims 52, 56 and 59 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al. (Hum. Gene Ther. 12:1103-1108; 2001), in view of Chang et al. (Curr. Gene Ther. 2:237-251; 2001). Applicants' cancellation of claims 50, 55 and 56 renders their rejections moot.

The rejections set forth on pp. 6-8 of the office action dated November 14, 2006, and pp. 4-6 of the previous office action dated August 3, 2007 are maintained for claims 35, 36 43-49, 51-54 and 57-67 for reasons of record.

Applicant's arguments concern the teachings of Barry, the primary reference shared by all the rejections set forth above. Applicants have traversed the rejections and re-state that Barry does not describe a vector wherein each of the two distinct posttranscriptional regulatory elements comprises a UTR region of a eukaryotic mRNA selected from a WPRE element, tau 3'UTR, TH3'UTR and APP5'UTR, and that synergistic effects could be obtained by combining at least two distinct posttranscriptional regulatory elements. Further stating that the inventors have tested combinations of these posttranscriptional regulatory elements and unexpectedly found that they could cooperate or synergize to provide positive effects on transgene expression (as confirmed by the Declaration under Rule 1.132, by Applicant Dr. Jacques Mallet), that is not taught by the cited prior art; and the secondary references are not believed to cure these deficiencies. Applicants' arguments have been fully considered, but not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The instant claims have been rejected over the reference of Barry et al. in view of the teachings of additional secondary references. There is no requirement that Barry et al. alone disclose each and every claimed element.

The Mallet Declaration states that the central polypurine tract (cPPT element) is not a posttranscriptional regulatory element because said elements have been shown to act by increasing nuclear transport of the virus preintegration complex and increasing transduction efficiency, and thus does not describe the synergistic effects of two distinct posttranscriptional regulatory elements. Such is not found persuasive, because while cPPT has been shown to increase nuclear transport and transduction efficiency, Barry et al. state that vectors encoding both the cPPT and post-transcriptional regulatory element provide enhanced transduction and transgene expression, than when present individually in a vector, further showing a 65-fold increase in EPO secretion when both PRE and cPPT were present (Title and Abstract). Therefore Barry et al. clearly describe synergy

between the elements in increasing transgene posttranscriptional expression; and thus further identify the cPPT as a posttranscriptional regulatory element.

As was indicated in the previous office actions, Barry et al. describe the generation of lentivirus vectors by combining several posttranscriptional regulatory elements that synergistically increase transgene expression. Barry et al. teach lentiviral vectors for provirus integration into nondividing mammalian cells, wherein the incorporation of two distinct posttranscriptional regulatory elements, namely a central polypurine tract (cPPT) and a human hepatitis virus posttranscriptional regulatory element (PRE; closely related to WPRE), that provide increased transgene expression in mammalian cells, and further provide the motivation to include two distinct posttranscriptional regulatory sequences, or to substitute or combine additional posttranscriptional regulatory elements with their vector, to increase transduction and stabilize virus vector mRNA for increased transgene expression (first column, p. 1104). The instantly claimed UTR elements are described in the secondary references, where their presence in the vector leads to increased transgene expression. As Barry et al. describe the synergistic effects obtained by combining two distinct posttranascriptional regulatory elements, it would have been obvious for a person of ordinary skill in the art to substitute any of the known UTR elements for the posttranscriptional regulatory element of Barry et al. (PRE) with a reasonable expectation of success.

It should therefore be noted that each of the claimed posttranscriptional regulatory elements comprising a UTR region and their respective functions was known in the prior art (as stated in the instant specification and admitted on the record by Applicants). That the combination of two posttranscriptional regulatory elements in a single vector encoding a transgene would synergistically increase transgene expression was taught by Barry et al. Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention by Applicants to combine any two of the known elements in a single vector, which amounts to simple substitution of one known element for another to yield predictable results.

The Mallet Declaration appears to additionally argue that the increased expression described by Barry et al. is less than would be predicted from the teachings of the

references by Zennou et al. However, such a comparison is flawed, because the Zennou et al. references describe cell transduction by HIV-1 DNA flap nuclear transporter, and do not address the effect of gene expression by the cPPT, as taught by Barry et al.

The Mallet Declaration further argues that the length of the PRE element of Barry et al. is over 1000 bp, and thus limited in its usefulness. Such is not found persuasive, because the Barry et al. reference has been applied to the instant claims for its teachings of a synergistic effect between two posttranscriptional elements in a viral vector, and it is the secondary references that provide the instantly claimed elements.

Therefore, the rejections are maintained for reasons of record and the foregoing discussion.

Conclusion

Claims 35, 36 43-49, 51-54 and 57-67 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, Art Unit 1633

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633